# Ocular involvement in adult and paediatric patients with monogenic autoinflammatory diseases: a Spanish multicentre retrospective study

A. Fonollosa[1-3], L. Pelegrín[4], S. García-Morillo[5], S. Buján-Rivas[6], L. Distefano[7], Á. Robles-Marhuenda[8], J. Fernández-Martín[9], A. González-García[10], Á. Garcia-Aparicio[11], N. Ortego-Centeno[12], V. Llorenç[4], M. Sainz de la Maza[4], C. Pinedo[13], B. Sopeña[14], L. Cocho[15], E. Carreño[16], R. Blanco[17], J. Antón[18], M. Pérez-Quintana[5], J.R. Marques-Soares[6], J. Artaraz[1], I. Ruiz-Arruza[19], A. Soto-Peleteiro[19], V. Gómez-Caverzaschi[20], O. Araújo[20], G. Espinosa[20], A. Adan[4], C. Fabiani[21], L. Cantarini[22], J. Hernández-Rodríguez[20], on behalf of the Spanish Society of Ocular Inflammation (SEIOC) and the AutoInflammatory Diseases Alliance (AIDA) Network

## Abstract

### Objective

*Ophthalmologic involvement in monogenic autoinflammatory diseases has been explored mainly in paediatric patients. The aim of this study is to characterise ophthalmologic manifestations, therapeutic management and visual outcomes in a Spanish (UVESAI) cohort of adult/paediatric patients with monogenic autoinflammatory diseases.*

### Methods

*Multicentre and retrospective study of patients with monogenic autoinflammatory diseases and ocular involvement. Eye manifestations, structural complications, treatments used and visual outcomes were analysed, and compared with previous studies.*

### Results

*Forty-six patients (44/2 adults/children; 21/25 adult/paediatric-onset) with monogenic autoinflammatory diseases [cryopyrin associated periodic syndromes (n=13/28.3%), mainly Muckle-Wells syndrome (MWS) (n=11/24%); familial Mediterranean fever (FMF) (n=12/26%); TNF receptor-associated periodic syndrome (TRAPS); (n=9/20%); Blau syndrome (n=8/17%); hyperimmunoglobulin D syndrome (HIDS) (n=2/4.3%), deficiency of adenosine deaminase-2 and NLRC4-Autoinflammatory disease] (one each) were included. Conjunctivitis (n=26/56.5%) and uveitis (n=23/50%) were the most frequent ocular manifestations. Twelve (26.1%) patients developed structural complications, being cataracts (n=11/24%) and posterior synechiae (n=10/22%) the most frequent. Conjunctivitis predominated in TRAPS, FMF, MWS and HIDS (mainly in adults), and uveitis, in Blau syndrome. Seven (8%) eyes (all with uveitis) presented with impaired visual acuity. Local and systemic treatment led to good visual outcomes in most patients. Compared with previous studies mainly including paediatric patients, less severe ocular involvement was observed in our adult/paediatric cohort.*

### Conclusion

*Conjunctivitis was the most common ocular manifestation in our TRAPS, FMF, MWS and HIDS patients, and uveitis predominated in Blau syndrome. Severe eye complications and poor visual prognosis were associated with uveitis. Adults with monogenic autoinflammatory diseases seem to exhibit a less severe ophthalmologic presentation than paediatric patients.*

**Key words**

ocular inflammation, monogenic autoinflammatory diseases, Blau syndrome, FMF, TRAPS, CAPS, HIDS, conjunctivitis, uveitis

*Affiliations: see page 2112.*

*Alex Fonollosa, MD*
*Laura Pelegrín, MD*
*Salvador García-Morillo, MD*
*Segundo Buján-Rivas, MD*
*Laura Distefano, MD*
*Ángel Robles-Marhuenda, MD*
*Julián Fernández-Martín, MD*
*Andrés González-García, MD*
*Ángel Garcia-Aparicio, MD*
*Norberto Ortego-Centeno, MD*
*Víctor Llorenç, MD*
*Maite Sainz de la Maza, MD*
*Carmen Pinedo, MD*
*Bernardo Sopeña, MD*
*Lidia Cocho, MD*
*Ester Carreño, MD*
*Ricardo Blanco, MD*
*Jordi Antón, MD*
*Marta Pérez-Quintana, MD*
*Joana R. Marques-Soares, MD*
*Joseba Artaraz, MD*
*Ioana Ruiz-Arruza, MD*
*Adriana Soto-Peleteiro, MD*
*Verónica Gómez-Caverzaschi, MD*
*Olga Araújo, MD*
*Gerard Espinosa, MD*
*Alfredo Adan, MD*
*Claudia Fabiani, MD*
*Luca Cantarini, MD*
*José Hernández-Rodríguez, MD*

*Please address correspondence to:*
*Alex Fonollosa*
*Department of Ophthalmology,*
*Hospital Universitario Cruces,*
*Plaza de Cruces s/n,*
*48903 Barakaldo, Spain.*
*E-mail: afonollosacalduch@gmail.com*

*and*
*José Hernández-Rodríguez*
*E-mail: jhernan@clinic.cat*

*Received on May 7, 2023; accepted in revised form on September 6, 2023.*



*Funding: J. Hernández-Rodríguez, V. Gómez-Caverzaschi and O. Araújo were supported by Instituto de Salud Carlos III (ISCIII) through the project PI21/01352 and co-funded by the European Union.*

*Competing interests: none declared.*

## Introduction

Monogenic autoinflammatory diseases comprise a group of rare diseases caused by genetic defects in inflammatory mechanisms that are characterised by recurrent or persistent episodes of fever accompanied by a variety of systemic and organ-specific manifestations and raised acute phase reactants (1, 2). Because of their inherited nature, they are usually manifested during childhood. However, disease onset may also occur in adult patients, which compared with paediatric patients, usually exhibits milder, incomplete or overlapping disease phenotypes and a predominance of unknown significance variants, somatic mutations and non-confirmatory genotypes (3-12). Monogenic conditions with adult-onset include familial Mediterranean fever (FMF), tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), cryopyrin-associated autoinflammatory syndromes (CAPS), Blau syndrome, and deficiency of adenosine deaminase 2 (DADA2) (3-6).

Ocular inflammatory lesions in monogenic autoinflammatory diseases may involve the ocular surface (eyelid and conjunctiva), sclera, cornea, uvea, retina, optic nerve, and adnexal and orbital structures, such as lacrimal gland and extraocular muscles. Corneal degenerative or dystrophic lesions, including keratoconus and retinitis pigmentosa-like disease have been occasionally reported (13, 14). Cataracts, glaucoma or choroidal neovascularisation can also occur as complications due to a persistent and/or uncontrolled ocular inflammation (13).

Ophthalmologic involvement has been reported in 1% of paediatric patients with FMF (15); conjunctivitis and periorbital oedema have been observed in 22% and 20% of patients with TRAPS, respectively (16); in CAPS and hyperimmunoglobulin D syndrome (HIDS), 71% and 17% of patients, respectively, may present with ocular manifestations, mainly conjunctivitis in both conditions (17, 18); and uveitis is the most common ocular lesion in Blau disease, observed in up to 80% of patients (19). Data about ocular involvement in other monogenic autoinflammatory diseases is currently scarce or absent.

The occurrence of ocular lesions in monogenic autoinflammatory disorders is usually accompanied by a diagnostic delay and subsequently, by a delay to start proper therapies to avoid irreversible structural complications and vision loss. Therefore, in order to increase its early recognition by ophthalmologists and other physicians, this study intended to compile a large series of Spanish adult and paediatric patients with monogenic autoinflammatory diseases and any type of ophthalmologic lesions with the aim to contribute to the characterisation of their ophthalmologic manifestations, therapeutic management and visual outcomes.

## Methods

*Study design and selection of patients*

The study was designed and led by the Group for the Study of Uveitis in Autoinflammatory Syndromes (UVESAI, for "*UVEitis en Síndromes AutoInflamatorios*") of the Spanish Society of Ocular Inflammation (SEIOC, for "*Sociedad Española de Inflamación Ocular*") and participating physicians included ophthalmologists, internists, paediatricians and rheumatologists who belonged to Spanish reference centres for autoimmune and autoinflammatory diseases. Several of the investigators were members of the AutoInflammatory Diseases Alliance Network (AIDA), which supported and collaborated with the study. Patients with monogenic autoinflammatory diseases and ocular manifestations controlled in the participant Spanish centres were retrospectively reviewed and included in the study. The period for inclusion of patients was June 2017 to February 2020.

Patients initially presenting with ocular manifestations at disease-onset and those previously diagnosed with autoinflammatory diseases already controlled by paediatric or adult physicians presenting with new ocular symptoms, were all ultimately assessed and diagnosed by ophthalmologists. Subsequent ophthalmological control visits were scheduled at physicians' convenience, and were more frequent in patients with uveitis. All the information about initial ocular lesions and posterior complications was retrospectively recorded from

initial and follow-up visits. However, visual acuity was only assessed at the visit nearby the inclusion on the study.
Only cases with clinical manifestations compatible with monogenic autoinflammatory diseases and a confirmatory genetic test were included. Patients had to fulfil the 2019 Eurofever/Paediatric Rheumatology INternational Trials Organisation (PRINTO) classification criteria for the main monogenic autoinflammatory conditions (FMF, TRAPS, HIDS and CAPS) (20). For other monogenic conditions not included in the 2019 Eurofever/PRINTO classification criteria, a definite diagnosis was accepted when a suggestive clinical presentation was accompanied by a causative mutation in the responsible gene previously described in The Registry of Hereditary Autoinflammatory Disorders Mutations (Infevers) (21). Those clinically suggestive patients without a positive genetic study and individuals with eye complaints but no systemic manifestations regardless of the genetic results were excluded. This study did not intend to collect all the patients with monogenic diseases from all the centres to draw epidemiological conclusions and only patients with these autoinflammatory conditions presenting with any ocular involvement were requested to be included.
This retrospective study was approved by the Ethics Committee of the Basque Country (project code: PI2016179). Patients' information was dissociated prior to analysis and all procedures were performed in accordance with the ethical principles expressed in the 2013 Declaration of Helsinki.

*Variables studied*
Variables collected included the type of monogenic autoinflammatory disease, sex, current age, age at first ocular and systemic symptoms, age at diagnosis of the ocular and systemic disease, systemic manifestations (including fever and serosal, musculoskeletal, mucocutaneous, gastrointestinal and neurologic involvement), genetic variants and causal genes, visual acuity (decimal scale) at the time of data collection, ocular laterality, ocular structural complications, ocular (local) procedures and systemic therapies administered at disease diagnosis and during the follow-up. The anatomic type of uveitis was evaluated by using the Standardization of Uveitis Nomenclature (SUN) classification criteria (22). Potential associations of monogenic autoinflammatory diseases with types of ocular involvement, structural complications and visual prognosis were also evaluated.

*Statistical study*
For qualitative variables, frequencies were used. Mean and standard deviations (SD) were calculated for quantitative variables following a normal distribution. Otherwise, median and interquartile ranges (IQR) [percentiles $25^{th}$ - $75^{th}$] were used. The Shapiro-Wilks test was applied to determine whether a quantitative variable followed a normal distribution. Associations between different parameters were analysed by using the test for equality of proportions with false discovery rate (FDR) correction. The data were analysed with the R Project for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria).

## Results

*Overall results*
Forty-six patients, 29 (63%) females and 17 (37%) males, were finally included and analysed. At the time of the study, 44 patients were adults ≥16 years and 2 children <16 years, with a median (IQR) age of 38.5 (26.5–48) years. Disease onset occurred at paediatric and adult age in 25 and 21 patients, respectively. The diagnosis of the autoinflammatory disease was established at paediatric age in 20 patients and during adulthood in 26 patients. Systemic manifestations started at a median (IQR) age of 16 (8–38.5) years and ocular symptoms occurred at a median (IQR) age of 16.5 years (11–38). With regard to the sequential presentation of symptoms, ocular complaints were the first manifestation of the autoinflammatory disease in 14 (30.4%) patients, occurred simultaneously in 15 (32.6%) cases, and after the systemic presentation in 17 (37%) patients. In the latter group, eye involvement occurred always with other systemic symptoms as part of the attacks. The definite diagnosis of monogenic autoinflammatory disease was established at a median (IQR) age of 23 (12–38) years (Table I).
CAPS was the monogenic autoinflammatory disease most commonly identified associated with ophthalmologic manifestations (n=13; 28.3%), followed by FMF (n=12; 26%), TRAPS (n=9; 19%), Blau syndrome (n=8; 17%) and HIDS (n=2; 4.4%). Two additional patients with DADA2 and NLRC4-associated disease (NLRC4-AD) and ocular involvement (one each) were identified. Among CAPS patients, most were diagnosed with Muckle-Wells syndrome (MWS) (n=11; 24%) and two patients (one each; 2.2%) with familiar cold-induced autoinflammatory syndrome (FCAS) and chronic infantile neurologic cutaneous articular - neonatal onset multi-inflammatory disease (CINCA-NOMID). Table I illustrates the chronologic presentation of systemic and ocular manifestations, and Supplementary Table S1 shows the results of the genetic studies of all patients included.
Overall, fever occurred in 26 (56.5%) patients, arthralgia/arthritis was present in 38 (82.6%) patients, cutaneous lesions in 35 (76.1%) and serosal involvement (mainly peritonitis and pericarditis) in 20 (43.5%) patients. Table II summarises the main systemic manifestations in every autoinflammatory condition.

*Type of ocular lesions*
The most frequent ophthalmologic manifestations were conjunctivitis (n=26; 56.5%) and uveitis (n=23; 50%), of which 16 (34.8%) were anterior and 7 (15.2%) were panuveitis. Keratitis, episcleritis, optic disk and periorbital oedema were less common ocular lesions. Thirty-six (78%) patients had bilateral ocular involvement and 19 (41%) suffered ocular lesions in two or more ocular structures. Table III shows the type and frequency of ocular involvement in our cohort.
With regard to the most frequent type of ocular involvement in every disease, conjunctivitis predominated in TRAPS (88.9%), FMF (66.7%) (Fig. 1A), CAPS (FCAS and MWS) (53.8%)

**Table I.** Type of monogenic autoinflammatory disease and chronological presentation of systemic and ophthalmologic manifestations in the present series.

| Monogenic autoinflammatory disease | N (%) | Sex (Female/ Male) | Current age (years)* | Age at systemic symptoms onset (years)* | Age at ocular symptoms onset (years)* | Age at disease diagnosis (years)* |
|---|---|---|---|---|---|---|
| CAPS | 13 (28.3) | 10/3 | 48 (38.5-60.5) | 14 (4.5-45) | 14 (7.5-39.5) | 34 (11.5-48) |
| *FCAS* | 1 (2.2) | 1/0 | 48 | 32 | | 47 48 |
| *MWS* | 11 (24) | 9/2 | 48 (42-61) | 14 (5-38) | 14 (8-38) | 39 (36-59) |
| *CINCA-NOMID* | 1 (2.2) | 0/1 | 35 | 0 | 10 | 12 |
| FMF | 12 (26) | 4/8 | 38 (20-48) | 16 (5-35) | 19 (12-41) | 30 (18-39) |
| TRAPS | 9 (20) | 4/5 | 37 (19-45) | 23.5 (12-38) | 23.5 (13-41) | 35 (15-40.5) |
| BLAU syndrome | 8 (17) | 7/1 | 29.5 25-36.5) | 3 (1-11) | 11.5 (0.9-16) | 12 (12-14) |
| HIDS | 2 (4.4) | 2/0 | 36 | 17.5 (3-32) | 25 (18-32) | 19.5 (5-34) |
| DADA | 21 (2.2) | 1/0 | 50 | 34 | 41 | 50 |
| NLRC4-AD | 1 (2.2) | 1/0 | 25 | 2 | 13 | 5 |
| **Total** | **46 (100)** | **29/17** | **38.5 (26.5-48)** | **16 (8-38.5)** | **16.5 (11-38)** | **23 (12-38)** |

* Results are expressed as median (IQR; 25%-75%)
CAPS: cryopyrin-associated autoinflammatory syndromes; CINCA-NOMID: chronic infantile neurologic cutaneous articular - neonatal onset multi-inflammatory disease; DADA2: deficiency of adenosine deaminase 2; FCAS: familiar cold-induced autoinflammatory syndrome; FMF: familial Mediterranean fever; HIDS: hyperimmunoglobulin D syndrome; MWS: Muckle-Wells syndrome; NLRC4-AD: NLRC4-associated disease; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.

**Table II.** Systemic manifestations of the 46 patients with monogenic autoinflammatory diseases and ocular involvement.

| Monogenic autoinflammatory disease | N (%) | Fever | Cutaneous | Arthralgia/arthritis | Serositis | Gastrointestinal | Neurologic |
|---|---|---|---|---|---|---|---|
| CAPS | 13 (28.3) | 5 (38) | 11 (84) | 11 (84) | 4 (30) | 2 (15) | 1 (7) |
| *FCAS* | 1 (2.2) | 0 (0) | 1 (100) | 1 (100) | 1 (100) | 1 (100) | 0 (0) |
| *MWS* | 11 (24) | 4 (36) | 9 (81) | 9 (81) | 3 (27) | 1 (9) | 0 |
| *CINCA-NOMID* | 1 (2.2) | 1 (100) | 1 (100) | 1 (100) | 0 (0) | 0 (0) | 1 (100) |
| FMF | 12 (26) | 11 (91) | 6 (50) | 8 (67) | 10 (83) | 6 (50) | 2 (17) |
| TRAPS | 9 (20) | 5 (55) | 8 (88) | 9 (100) | 2 (22) | 4 (44) | 1 (1) |
| BLAU syndrome | 8 (17) | 1 (12.5) | 7 (88) | 8 (100) | 1 (12.5) | 0 (0) | 0 |
| HIDS | 2 (4.4) | 2 (100) | 1 (50) | 1 (50) | 1 (50) | 2 (100) | 0 |
| DADA2 | 1 (2.2) | 1 (100) | 1 (100) | 1 (100) | 1 (100) | 0 (0) | 0 (0) |
| NLRC4-AD | 1 (2.2) | 1 (100) | 1 (100) | 0 (0) | 1 (100) | 0 (0) | 0 (0) |
| **Total** | **46 (100)** | **26 (56.5)** | **35 (76.1)** | **38 (82.6)** | **20 (43.5)** | **14 (30.4)** | **4 (8.7)*** |

CAPS: cryopyrin-associated autoinflammatory syndromes; CINCA-NOMID: chronic infantile neurologic cutaneous articular - neonatal onset multi-inflammatory disease; DADA2: deficiency of adenosine deaminase 2; FCAS: familiar cold-induced autoinflammatory syndrome; FMF: familial Mediterranean fever; HIDS: hyperimmunoglobulin D syndrome; MWS: Muckle-Wells syndrome; NLRC4-AD: NLRC4-associated disease; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.
*Meningitis was presented by 4 (8.7) patients (2 with FMF, 1 with TRAPS and 1 with CINCA-NOMID and 1 (2.3%) patient with CINCA-NOMID suffered encephalitis.

and HIDS (100%). Uveitis was present in all patients with Blau syndrome, and less frequently in other monogenic conditions (CAPS [MWS and CINCA-NOMID] 53.8%, HIDS 50%, and TRAPS 22.2%). Patients with NLRC4-AD and DADA2 (one each) presented uveitis as the only ocular manifestation. In terms of uveitis anatomical classification, anterior uveitis was present 16 patients [4 with Blau syndrome, 6 with CAPS-MWS (Fig. 1B), 2 with FMF, and one each with TRAPS, HIDS, DADA2 and NLRC4-AD), and panuveitis was detected in 4 patients with Blau syndrome (one of them with multifocal choroiditis] (Fig. 1C-E) and 1 patient each with FMF, TRAPS and CAPS-CINCA-NOMID. No cases of intermediate and posterior uveitis were registered.

Keratitis and episcleritis were observed in 38.5% and 30.8% of CAPS (only MWS) patients, respectively, and both lesions were reported in 50% of HIDS and 16.7% of FMF patients. Optic disk oedema was observed in 1 (8.3%) patient with FMF, and periocular oedema in 1 (11.1%) patient with TRAPS and 1 (7.7%) patient with CAPS-FCAS.

The study of potential associations between ocular lesions and the type of monogenic autoinflammatory diseases revealed that conjunctivitis was significantly associated with TRAPS ($p$=0.002) and uveitis with Blau syndrome ($p$=0.005). No other associations were found.

*Type of ocular lesion according to the age at disease onset*

Conjunctivitis was more frequently presented in patients in whom the autoinflammatory disease was initiated at adult age compared with patients with paediatric onset 16 (76.2%) *vs*. 10 (40%) patients; $p$-value = 0.013. Contrarily, uveitis of any type was more commonly presented by children [18 (72%) *vs*. 5 (23.8%) patients; $p$-value = 0.001], and panuveitis was only ob-

**Table III.** Ocular involvement in patients with monogenic autoinflammatory diseases.

| Monogenic autoinflammatory disease | N (%) | Conjunctivitis | Uveitis (total) | Panuveitis | Keratitis | Episcleritis | Periorbital oedema | Optic disk oedema |
|---|---|---|---|---|---|---|---|---|
| CAPS | 13 (28.3) | 7 (53.8) | 7 (53.8) | 1 (7.7) | 5 (38.5) | 4 (30.8) | 1 (7.7) | 0 (0) |
| *FCAS* | 1 (2.2) | 1 (100) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (100) | 0 (0) |
| *MWS* | 11 (24) | 6 (54.5) | 6 (54.5) | 0 (0) | 5 (45.5) | 4 (36.4) | 0 (0) | 0 (0) |
| *CINCA-NOMID* | 1 (2.2) | 0 (0) | 1 (100) | 1 (100) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| FMF | 12 (26) | 8 (66.7) | 3 (25) | 1 (8.3) | 2 (16.7) | 2 (16.7) | 0 (0) | 1 (8.3) |
| TRAPS | 9 (20) | 8 (88.9) | 2 (22.2) | 1 (11.1) | 0 (0) | 0 (0) | 1 (11.1) | 0 (0) |
| BLAU syndrome | 8 (17) | 1 (12.5) | 8 (100) | 4 (50) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| HIDS | 2 (4.4) | 2 (100) | 1 (50) | 0 (0) | 1 (50) | 1 (50) | 0 (0) | 0 (0) |
| DADA2 | 1 (2.2) | 0 (0) | 1 (100) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| NLRC4-AD | 1 (2.2) | 0 (0) | 1 (100) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Total** | **46 (100)** | **26 (56.5)** | **23 (50)** | **7 (15.2)** | **8 (17.4)** | **7 (15.2)** | **2 (4.3)** | **1 (2.2)** |

CAPS: cryopyrin-associated autoinflammatory syndromes; CINCA-NOMID: chronic infantile neurologic cutaneous articular - neonatal onset multi-inflammatory disease; DADA2: deficiency of adenosine deaminase 2; FCAS: familiar cold-induced autoinflammatory syndrome; FMF: familial Mediterranean fever; HIDS: hyperimmunoglobulin D syndrome; MWS: Muckle-Wells syndrome; NLRC4-AD: NLRC4-associated disease; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.

served in patients with paediatric onset ($p$-value = 0.009). The remaining ocular signs did not differ between groups (Supplementary Table S2).

*Structural ocular complications*

Complications affecting ocular structures were developed by 12 (26.1%) patients, and 7 (15%) subjects had more than one structural complication. The most frequent complication were cataracts (n=11; 24%), posterior synechiae (n=10; 22%) (Fig. 1C-D) and band keratopathy and glaucoma (n=3; 6.5% each). Choroidal neovascularisation (Fig. 1F), macular oedema, chorioretinal scars and corneal leukoma were less commonly observed.

Structural complications were observed mainly in patients with Blau syndrome, CAPS and FMF. Table IV illustrates the type and frequency of ocular complications in every condition. An association between baseline ocular lesions and structural complications was only found for uveitis and cataract ($p$=0.02).

*Visual acuity*

With regard to the visual acuity at the inclusion in the study, impaired visual acuity (<0.5) was observed in 7 eyes, all of them with previous uveitis (2 eyes with panuveitis and 3 eyes with anterior uveitis due to Blau syndrome, and 2 eyes with panuveitis due to CAPS-CINCA-NOMID). The only ocular lesion associated with loss of vision (<0.5) was uveitis ($p$=0.003). Overall, the median (IQR) final visual acuity in the involved eyes was 1 (0.92-1) in the right eye, and 1 (0.8-1) in the left eye.

*Therapeutic management*

*Local therapy.* The most commonly used ocular treatments were non-steroidal anti-inflammatory drugs and/or glucocorticoids eye drops, administered in 41 (89.1%) patients. Periocular or intraocular glucocorticoids were injected to 5 (10.9%) patients and intravitreal injections of bevacizumab, an antiangiogenic agent, was administered to 1 (2.2%) patient with Blau syndrome and choroidal neovascularisation. These local procedures were mainly used in combination with the baseline systemic therapy required for control the systemic manifestations of the autoinflammatory disease.

*Systemic therapy.* At the moment of data collection, 4 (8.7%) patients were not receiving any treatment and the remaining patients were being treated only with colchicine (n=7; 15.2%) or prednisone (n=1; 2.1%), conventional immunosuppressive drugs (including methotrexate, azathioprine and tacrolimus alone or combined with prednisone and/or colchicine or biologic agents) (n=3; 6.5%), and anti-cytokine agents alone or in combination with conventional immunosuppressive drugs (n=32; 69.6%). Biologic agents used were interleukin (IL)-1 blockers (anakinra or canakinumab), anti-TNF agents (adalimumab, etanercept and certolizumab), anti-IL-6 agent (tocilizumab) and Janus kinase (JAK) inhibitor (tofacitinib). All treatment modalities are detailed in Supplementary Table S3.

With regard to previous treatment lines, 27 (58.7%) patients had been treated with conventional immunosuppressive drugs, and 32 (69.6%) subjects had received biologic agents, including IL-1 blockers (n=26; 56.5%), anti-TNF agents (n=10; 21.7%) and tocilizumab (n=1; 2.2%).

In 15 (32%) patients with severe or relapsing ocular lesions despite previous systemic therapy or local procedures, systemic agents (usually more than one) were used with good control of ophthalmologic manifestations. These drugs included colchicine (n=2; 4.3%), conventional immunosuppressive drugs, mainly methotrexate (n=9; 19.6%), TNF inhibitors (n=7; 15.2%), and anti-IL-1 agents (n=6; 13%).

## Discussion

The UVESAI cohort represents the first multicentre and multidisciplinary Spanish study exploring ophthalmologic manifestations and outcomes in adult and paediatric patients with monogenic autoinflammatory diseases.

In a recent systematic review including 1,353 patients (most of them paediatric) with monogenic autoinflammatory diseases and ocular involvement, systemic disease onset occurred prior to ocular manifestations, which were pre-

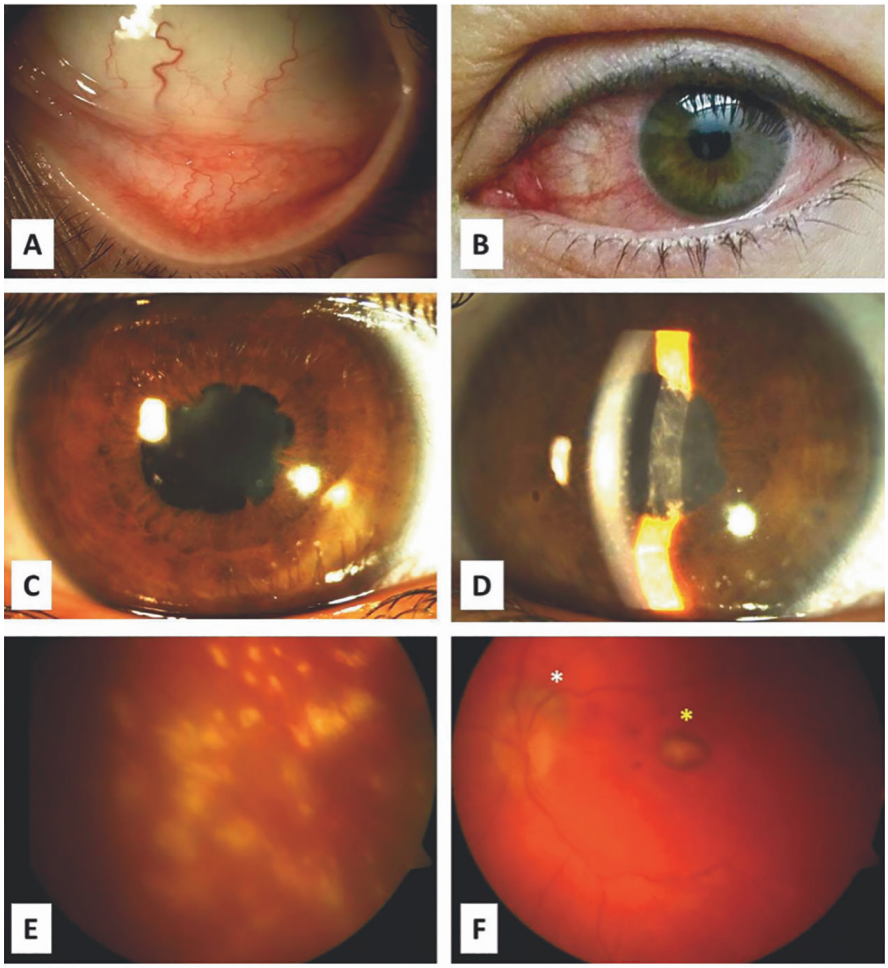


**Fig. 1.** Ocular manifestations in patients with monogenic autoinflammatory diseases: **A**) Conjunctivitis (from a patient with familial Mediterranean fever); typical conjunctival hyperaemia with follicular reaction is observed; **B**) Anterior uveitis (from a patient with Muckle-Wells syndrome): the figure shows a typical ciliary hyperaemia; **C** and **D**) Posterior synechiae (from a patient with Blau syndrome): 360º posterior synechiae are observed, along with granulomatous keratic precipitates and lens anterior capsule opacification; **E**) Multifocal choroiditis lesions (from a patient with Blau syndrome); and **F**) Choroidal neovascularization as a structural complication in a patient with Blau syndrome, involving juxtapapilar (white asterisk) and macular (yellow asterisk) areas.

sented at a mean age of 5 and 9 years, respectively (14). In our patients, systemic symptoms similarly occurred after, before or simultaneously than ophthalmologic manifestations (a third each), at a median (IQR) age of 16 (8–38.5) and 16.5 (11–38) years, respectively. Because of the high proportion of adult patients included in our cohort, the simultaneous presentation of ocular and systemic symptoms or the initial occurrence of the ocular involvement could also be interpreted as a particular feature of the adult onset of monogenic autoinflammatory diseases. However, this could be also due to a delayed diagnosis because of the under-recognition of some manifestations of autoinflammatory diseases in adult patients.

In CAPS, eye involvement has been reported in 71% of patients (in 97 out 136 cases) in the Eurofever Registry (17), and in 78% of MWS patients (23). In 680 CAPS patients with ocular involvement, systemic and ocular manifestations occurred sequentially at a mean age of 5.6 and 12 years, respectively (14). Conjunctivitis was the most frequent ocular lesion in 62.4% of cases, followed by uveitis (28.4%) (anterior [19.1%], posterior [0.7%], and intermediate uveitis [0.3%] and panuveitis [0.3%]), papillitis or papilloedema (27%), keratitis (10.6%), episcleritis (2.2%), multifocal choroiditis (1.9%), retinal vasculitis/retinitis (1.3%/0.4%) and periorbital oedema (1%) (14). Most of our CAPS patients were diagnosed with MWS and disease onset occurred at 5 years or older. Among them, 53.8% each presented with conjunctivitis and uveitis, followed by keratitis (38.5%), episcleritis (30.8%) and periorbital oedema (7.7%).

Ocular complications in CAPS patients have been described to occur as optic nerve atrophy (7.4%), cataract (1.6%), band keratopathy (1.2%), glaucoma (0.6%), choroidal thickness reduction (0.6%), retinal detachment (0.3%) and corneal perforation (0.1%) (14). Other seldom ocular manifestations reported include retinal dystrophy, choroidal mass, nystagmus, ectopia pupillae, aphakia and keratoconus (14). In our CAPS patients, ophthalmologic complications included cataract (15.3%), posterior synechiae (23%), and band keratopathy and corneal leukoma (7% each).

In FMF, ocular involvement has been described in about 1% of cases in a series of 512 paediatric FMF patients (15). A review of 211 FMF patients with a mean age at disease onset of 13 years and ocular manifestations occurring at a mean age of 19 years, revealed the occurrence of retinal vasculitis (31.3%) and uveitis (10.4%) (anterior [6.6%], posterior [1,4%], and intermediate uveitis [1%], and panuveitis [0.1%]). Papillitis, optic neuritis, episcleritis and periorbital oedema have also been reported in isolated cases (14). A decrease of choroidal thickness is the most common ocular complication in FMF, detected in almost half of cases (14), and has also been described in adult patients with FMF (24). In our FMF patients, the mean age at systemic and ocular presentation were of 16 and 19 years, respectively. Among them, conjunctivitis was presented by 66.7% of cases, followed by uveitis (25%), keratitis and episcleritis (16.7% each), and optic disk oedema (8.3%). The high proportion of conjunctivitis in our FMF series (affecting two third of patients) had not been previously described (14), except in a single case from a Chinese FMF series (25). The significant predominance of conjunctivitis in adults and the absence of more severe ocular manifestations in our cohort might be related to the milder presentation of FMF during the adult-

**Table IV.** Structural complications in patients with monogenic autoinflammatory diseases and ocular involvement.

| Monogenic autoinflammatory disease | N (%) | Cataract | Posterior synechiae | Band keratopathy | Glaucoma | Choroidal neovascularisation | Macular oedema | Chorioretinal scars | Corneal leukoma |
|---|---|---|---|---|---|---|---|---|---|
| CAPS | 13 (28.3) | 2 (15.3) | 3 (23) | 1 (7) | 0 | 0 | 0 | 0 | 1 (7) |
| FCAS | 1 (2.2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| MWS | 11 (24) | 1 (9) | 2 (18) | 0 | 0 | 0 | 0 | 0 | 1 (9) |
| CINCA-NOMID | 1 (2.2) | 1(100) | 1(100) | 1(100) | 0 | 0 | 0 | 0 | 0 |
| FMF | 12 (26) | 1 (8) | 1(8) | 0 | 0 | 0 | 0 | 0 | 0 |
| TRAPS | 9 (20) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| BLAU syndrome | 8 (17) | 7 (88) | 6 (75) | 2 (25) | 3 (37.5) | 1 (12.5) | 1(12.5) | 1(12.5) | 0 |
| HIDS | 2 (4.4) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DADA2 | 1 (2.2) | 1 (100) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| NLRC4-AD | 1 (2.2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | 46 (100) | 11 (24) | 10 (22) | 3 (6.5) | 3 (6.5) | 1 (2.2) | 1 (2.2) | 1 (2.2) | 1 (2.2) |

CAPS: cryopyrin-associated autoinflammatory syndromes; CINCA-NOMID: chronic infantile neurologic cutaneous articular - neonatal onset multi-inflammatory disease; DADA2: deficiency of adenosine deaminase 2; FCAS: familiar cold-induced autoinflammatory syndrome; FMF: familial Mediterranean fever; HIDS: hyperimmunoglobulin D syndrome; MWS: Muckle-Wells syndrome; NLRC4-AD: NLRC4-associated disease; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.

hood, as previously described for other systemic manifestations (3-7).

Ophthalmologic complications in FMF are infrequent. While corneal ectasia is described in 6.2% of cases, other secondary lesions, such as cataract, glaucoma, posterior synechiae, band keratopathy, cystoid macular oedema, retinal detachment, corneal perforation and oculomotor nerve palsy have been scarcely reported (14). In our series, FMF patients developed few ocular complications, since cataract and posterior synechiae were detected in only 8% of cases.

In TRAPS, the most common ocular complaints are conjunctivitis and periorbital oedema occurring in 22% and 20% of a series of 158 patients with TRAPS from the Eurofever registry, respectively (16). In addition, conjunctivitis and periorbital oedema tended to be more frequent in paediatric patients than in those with an adult-onset, and in patients with structural mutations than in those carrying low-penetrant variants, such as R92Q (3, 16). No differences between age of presentation and ocular manifestations have been detected in patients with R92Q-associated TRAPS (10). A review of 138 patients with TRAPS and ocular involvement, at a mean disease onset of 12.5 years, conjunctivitis (56.5%) and periorbital pain/oedema (47.8%) were the most frequent ocular manifestations (14). Multifocal choroiditis, panuveitis and optic neuritis have also been reported in isolated cases with TRAPS (14). All our TRAPS patients carried the R92Q variant, and the mean age at disease onset was 23.5 years. Most patients (88.9%) presented with conjunctivitis, followed by uveitis (22.2%) and periorbital oedema (8.3%). Compared to TRAPS patients from previous studies (14), our patients were older and presented more frequently with conjunctivitis and less often with periorbital oedema.

Regarding eye complications in TRAPS, cataract, posterior synechiae and glaucoma have been reported only in 0.7% of patients with ocular involvement. Similarly, none of our TRAPS patients developed ocular complications during the follow-up.

In Blau syndrome, ocular involvement occurs as part of the classic triad of arthritis, dermatitis and uveitis (19, 26). A review of 238 patients with Blau syndrome and ocular lesions described the occurrence of ocular symptoms at a mean of 9 years, after a mean of 5 years from disease onset (14). Uveitis, mainly described as granulomatous, occurred in 95.4% of patients. Among uveitis, 48% were anterior, 43.6% panuveitis, 11.9% posterior and 2.6% intermediate (14). Other less frequent ocular lesions included multifocal choroiditis (15.1%), papilitis/papilloedema (10.9%), keratitis (6.3%), episcleritis (1.3%) and ocular myositis (0.4%) (14). Our patients with Blau syndrome shared similar age at the onset of systemic and ocular presentation than in those previously reported (14). While all subjects presented with uveitis (50% with panuveitis), conjunctivitis was less often (12.5%) manifested.

Late eye complications in Blau syndrome are commonly associated with the severity of uveitis and include cataract (23.9%), glaucoma (9.7%), cystoid macular oedema (8%), retinal detachment (1.7%) and optic atrophy (3.8%). Other less frequent ocular lesions include choroidal thickness reduction, corneal perforation, and chorioretinal hypopigmentation (14). In our series, patients with Blau syndrome presented with the highest rate of ocular complications among all monogenic autoinflammatory diseases. The most frequent structural complications were cataract (88%), posterior synechiae (75%), glaucoma (37.5%) and band keratopathy (25%). Choroidal neovascularisation, chorioretinal scars and macular oedema were severe lesions only observed in a patient with Blau syndrome.

There is scarce information about ocular manifestations in the remaining monogenic autoinflammatory diseases. In HIDS, ocular involvement occurs in 17% of patients as conjunctivitis (10%), uveitis (2%) and cataract (3%) (18). Retinal dystrophy (27, 28), retinal degeneration and, diffuse retinal haemorrhages (28), as well as nummular keratitis evolving to a large corneal scar and decreased vision (29) have also been described. Our two HIDS patients suffered conjunctivitis, anterior uveitis,

keratitis and episcleritis, and no structural complications were observed. In DADA2, a reduction in choroidal thickness, strabismus, retinal vasculitis and optic neuritis have been observed in few patients (14). Our DADA2 patient presented with anterior uveitis and also developed cataract. In NLRC4-AD, conjunctivitis, episcleritis, keratitis and dry eye have been reported in 42% of patients in a series with 26 NLRC4-AD patients. These ocular manifestations clearly predominated in the subgroup with skin and articular involvement (30). Our patient with NLRC4-AD (with cutaneous and serosal lesions) presented with anterior uveitis and no ocular complications.

Regarding therapeutic approaches, most patients received local treatment, mainly anti-inflammatory and glucocorticoids drops. While 8.7% of patients did not require any treatment and 17.3% were only treated with colchicine or prednisone alone, biologic therapy was administered to two-third of patients. Among biologic agents, those more frequently used were IL-1 blockers in almost half of patients and anti-TNF agents in 17.4% of cases. Systemic treatment for managing ocular involvement was administrated to a third of patients.

Visual outcomes were in general favourable due to a low rate of severe structural complications, which were confined to a single case with Blau syndrome presenting with uveitis and choroidal neovascularisation. Cataract or glaucoma, as less severe complications, were all presented by patients previously suffering uveitis.

Limitations of this retrospective study include the overall small number of patients recruited and the reduced proportion of paediatric patients, despite the predominance of monogenic autoinflammatory diseases in paediatric population. This bias was due to the fact that most patients were controlled by adult physicians at the time of the study. However, there is still a remarkable representation of paediatric patients since more than half of patients initiated autoinflammatory manifestations during childhood. Due to the retrospective nature of this multicentre study, visual acuity was assessed at the moment of the study (and not at the onset of the ocular involvement), after a variable follow-up. In addition, the fact that the ocular involvement was assessed only in symptomatic patients might have led to underestimate the number of patients with subclinical ocular involvement, in particular of those infants with uveitis, since their inability to refer specific symptoms. Overall, the under-recognition of many of the included monogenic autoinflammatory diseases and others in which ocular involvement is remarkable, such as A20 haploinsufficiency, has probably contributed to misrepresent the results.

In conclusion, ophthalmologic involvement in monogenic autoinflammatory diseases affecting adult and paediatric patients differs from the ocular presentation described in studies mainly based on paediatric population. Compared with those features described in children, in whom a sequential presentation of systemic followed by ocular symptoms is common, adults tend to present similarly with sequential or simultaneous presentations of both ocular and systemic symptoms. Conjunctivitis and uveitis are the most common ocular lesions in our mixed cohort of patients with monogenic autoinflammatory diseases. While conjunctivitis is clearly associated with an adult presentation and prevails as the most frequent ocular complaint in TRAPS, FMF, CAPS and HIDS patients, uveitis remains the typical feature of Blau syndrome. Structural ocular complications and visual impairment are associated with uveitis. The high proportion of adults in the UVE-SAI cohort and the predominance of conjunctivitis (mainly in adult patients) with an overall good visual prognosis could be in part reflecting the less severe or incomplete presentation of monogenic autoinflammatory diseases in adults compared to those patients with paediatric onset. However, our results should be confirmed in future larger multicentre and international registry studies.

**Affiliations**

[1]Department of Ophthalmology, BioCruces Bizkaia Health Research Institute, Cruces University Hospital, University of the Basque Country, Barakaldo; [2]Instituto Oftalmológico Bilbao; [3]Cooperative Health Network for Research in Ophthalmology (Oftared), National Institute of Health Carlos III, ISCIII, Madrid; [4]Department of Ophthalmology, Institut Clínic d'Oftalmologia (ICOF), Hospital Clinic de Barcelona, University of Barcelona, Institut de Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona; [5]Autoimmune and Rare Diseases Unit, Department of Internal Medicine, Hospital Virgen del Rocío, Center of the Centros, Servicios y Unidades de Referencia (CSUR) in Autoinflammatory Diseases, Sevilla; [6]Autoinflammatory Diseases Unit, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Center of the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA), Spanish Center of the Centros, Servicios y Unidades de Referencia (CSUR) and Catalan Center of the Xarxa d'Unitats d'Expertesa Clínica (XUEC) for Autoinflammatory Diseases, Barcelona; [7]Department of Ophthalmology, Hospital Vall d'Hebron, Barcelona; [8]Systemic Autoimmune Diseases Unit, Department of Internal Medicine, Hospital Universitario La Paz, Madrid; [9]Department of Internal Medicine, Hospital do Meixoeiro-Chuvi, Rare Diseases and Paediatric Medicine Group, Galicia Sur Health Research Institute (IIS Galicia Sur), Vigo, Pontevedra; [10]Department of Internal Medicine, Autoimmune and Rare Diseases Unit, Hospital Universitario Ramón y Cajal, Universidad de Alcalá de Henares, IRYCIS, Madrid; [11]Division of Rheumatology, Hospital de Toledo; [12]Systemic Autoimmune Diseases Unit, Department of Internal Medicine, Hospital Universitario San Cecilio, University of Granada; [13]Paediatric Rheumatology Unit, BioCruces Bizkaia Health Research Institute, Cruces University Hospital, University of the Basque Country, Barakaldo; [14]Department of Internal Medicine, Complejo Hospitalario Universitario de Santiago, University of Santiago de Compostela; [15]Department of Ophthalmology, Hospital Clínico Universitario de Valladolid, Institute of Applied OphthalmoBiology (IOBA), University of Vallado-

lid; [16]Department of Ophthalmology, Fundación Jiménez Díaz University Hospital, Madrid; [17]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander; [18]Division of Paediatric Rheumatology, Paediatric Immune Dysfunction Disease Study Group (GEMDIP), Institut de Recerca Sant Joan de Déu, Hospital Sant Joan de Déu, Center of the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA), Spanish Center of the Centros, Servicios y Unidades de Referencia (CSUR) and Catalan Center of the Xarxa d'Unitats d'Expertesa Clínica (XUEC) for Autoinflammatory Diseases, Esplugues de Llobregat, Barcelona; [19]Autoimmune Diseases Research Unit, Department of Internal Medicine, Biocruces Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, Barakaldo; [20]Autoinflammatory Diseases Clinical Unit and Vasculitis Research Unit, Department of Autoimmune Diseases, Hospital Clínic de Barcelona, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Center of the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA), Spanish Center of the Centros, Servicios y Unidades de Referencia (CSUR) and Catalan Center of the Xarxa d'Unitats d'Expertesa Clínica(XUEC) for Autoinflammatory Diseases, Barcelona, Spain; [21]Ophthalmology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena, Center of the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA), Siena, Italy; [22]Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Center of the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA), Siena, Italy.

## References

1. KASTNER DL, AKSENTIJEVICH I, GOLDBACH-MANSKY R: Autoinflammatory disease reloaded: a clinical perspective. *Cell* 2010; 140: 784-90. https://doi.org/10.1016/j.cell.2010.03.002
2. AKSENTIJEVICH I, SORIANO A, HERNÁNDEZ-RODRÍGUEZ J: Autoinflammatory Diseases: From Genes to Bedside. *Front Immunol* 2020; 11: 1177. https://doi.org/10.3389/fimmu.2020.01177
3. HERNÁNDEZ-RODRÍGUEZ J, RUÍZ-ORTIZ E, TOMÈ A *et al*.: Clinical and genetic characterization of the autoinflammatory diseases diagnosed in an adult reference center. *Autoimmun Rev* 2016; 15: 9-15. https://doi.org/10.1016/j.autrev.2015.08.008
4. CANTARINI L, RIGANTE D: Adult-onset autoinflammatory disorders: a still debated entity? *Clin Exp Rheumatol* 2015; 33: 137-40.
5. MUSCARI I, IACOPONI F, CANTARINI L *et al*.: The diagnostic evaluation of patients with potential adult-onset autoinflammatory disorders: our experience and review of the literature. *Autoimmun Rev* 2012; 12: 10-3. https://doi.org/10.1016/j.autrev.2012.07.015
6. HERNÁNDEZ-RODRÍGUEZ J, RUIZ-ORTIZ E, YAGÜE J: Monogenic autoinflammatory diseases: General concepts and presentation in adult patients. *Med Clin* (Barc) 2018; 150: 67-74. https://doi.org/10.1016/j.medcli.2017.07.012
7. SAYARLIOGLU M, CEFLE A, INANC M *et al*.: Characteristics of patients with adult-onset familial Mediterranean fever in Turkey: analysis of 401 cases. *Int J Clin Pract* 2005; 59: 202-5. https://doi.org/10.1111/j.1742-1241.2004.00294.x
8. COMAK E, AKMAN S, KOYUN M *et al*.: Clinical evaluation of R202Q alteration of MEFV genes in Turkish children. *Clin Rheumatol* 2014; 33: 1765-71. https://doi.org/10.1007/s10067-014-2602-6
9. CANTARINI L, RIGANTE D, MERLINI G *et al*.: The expanding spectrum of low-penetrance TNFRSF1A gene variants in adults presenting with recurrent inflammatory attacks: clinical manifestations and long-term follow-up. *Semin Arthritis Rheum* 2014; 43: 818-23. https://doi.org/10.1016/j.semarthrit.2013.12.002
10. RUIZ-ORTIZ E, IGLESIAS E, SORIANO A *et al*.: Disease phenotype and outcome depending on the age at disease onset in patients carrying the R92Q low-penetrance variant in TNFRSF1A gene. *Front Immunol* 2017; 8: 299. https://doi.org/10.3389/fimmu.2017.00299
11. NASELLI A, PENCO F, CANTARINI L *et al*.: Clinical characteristics of patients carrying the Q703K variant of the NLRP3 gene: a 10-year multicentric national study. *J Rheumatol* 2016; 43: 1093-100. https://doi.org/10.3899/jrheum.150962
12. TOPLAK N, FRENKEL J, OZEN S *et al*.: An international registry on autoinflammatory diseases: the Eurofever experience. *Ann Rheum Dis* 2012; 71: 1177-82. https://doi.org/10.1136/annrheumdis-2011-200549
13. SOTA J, VITALE A, FABIANI C *et al*.: The eye involvement in monogenic autoinflammatory diseases: literature review and update. *Clin Exp Rheumatol* 2018; 36 (Suppl. 110): S44-53
14. MACCORA I, MARRANI E, MASTROLIA MV *et al*.: Ocular involvement in monogenic autoinflammatory disease. *Autoimmun Rev* 2021; 20: 102944. https://doi.org/10.1016/j.autrev.2021.102944
15. AVAR-AYDIN PO, CAKAR N, OZCAKAR ZB, YALCINDAG N, YALCINKAYA F: Ocular inflammatory diseases in children with familial Mediterranean fever: a true association or a coincidence? *Int Ophthalmol* 2022; 42: 1249-57. https://doi.org/10.1007/s10792-021-02111-6
16. LACHMANN HJ, PAPA R, GERHOLD K *et al*.: The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. *Ann Rheum Dis* 2014; 73: 2160-7. https://doi.org/10.1136/annrheumdis-2013-204184
17. LEVY R, GERARD L, KUEMMERLE-DESCHNER J *et al*.: Phenotypic and genotypic characteristics of cryopyrin-associated periodic syndrome: a series of 136 patients from the Eurofever Registry. *Ann Rheum Dis* 2015; 74: 2043-9. https://doi.org/10.1136/annrheumdis-2013-204991
18. TER HAAR NM, JEYARATNAM J, LACHMANN HJ *et al*.: The phenotype and genotype of mevalonate kinase deficiency: A series of 114 cases from the Eurofever Registry. *Arthritis Rheumatol* 2016; 68: 2795-805. https://doi.org/10.1002/art.39763
19. ROSE CD, WOUTERS CH, MEIORIN S *et al*.: Pediatric granulomatous arthritis: an international registry. *Arthritis Rheum* 2006; 54: 3337-44. https://doi.org/10.1002/art.22122
20. GATTORNO M, HOFER M, FEDERICI S *et al*.: Classification criteria for autoinflammatory recurrent fevers. *Ann Rheum Dis* 2019; 78: 1025-32. https://doi.org/10.1136/annrheumdis-2019-215048
21. MILHAVET F, CUISSET L, HOFFMAN HM *et al*.: The infevers autoinflammatory mutation online registry: update with new genes and functions. *Hum Mutat* 2008; 29: 803-8. https://doi.org/10.1002/humu.20720
22. JABS DA, NUSSENBLATT RB, ROSENBAUM JT *et al*.: Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005; 140: 509-16. https://doi.org/10.1016/j.ajo.2005.03.057
23. KUMMERLE-DESCHNER JB, TYRRELL PN, REESS F *et al*.: Risk factors for severe Muckle-Wells syndrome. *Arthritis Rheum* 2010; 62: 3783-91. https://doi.org/10.1002/art.27696
24. BICER T, CELIKAY O, KOSKER M *et al*. Retinal and choroidal thickness in adult patients with familial Mediterranean fever. *Ophthalmic Epidemiol* 2017; 24: 346-51. https://doi.org/10.1080/09286586.2017.1294697
25. WU D, SHEN M, ZENG X: Familial Mediterranean fever in Chinese adult patients. *Rheumatology* (Oxford) 2018; 57: 2140-4. https://doi.org/10.1093/rheumatology/key218
26. SURESH S, TSUI E: Ocular manifestations of Blau syndrome. *Curr Opin Ophthalmol* 2020; 31: 532-7. https://doi.org/10.1097/icu.0000000000000705

27. PRIETSCH V, MAYATEPEK E, KRASTEL H *et al*.: Mevalonate kinase deficiency: enlarging the clinical and biochemical spectrum. *Pediatrics* 2003; 111: 258-61. https://doi.org/10.1542/peds.111.2.258
28. BRENNENSTUHL H, NASHAWI M, SCHROTER J *et al*.: Phenotypic diversity, disease progression, and pathogenicity of MVK missense variants in mevalonic aciduria. *J Inherit Metab Dis* 2021; 44: 1272-87. https://doi.org/10.1002/jimd.12412
29. KRAUS CL, CULICAN SM: Nummular keratopathy in a patient with Hyper-IgD syndrome. *Pediatr Rheumatol Online J* 2009; 7: 14. https://doi.org/10.1186/1546-0096-7-14
30. RODRIGUES F, HENTGEN V, BACHMEYER C *et al*.: [NLRC4 associated autoinflammatory diseases: A systematic review of the current literature]. *Rev Med Interne* 2018; 39: 279-86. https://doi.org/10.1016/j.revmed.2018.02.003